POST TRANSPLANT NEPHROTIC SYNDROME– CLINICOPATHOLOGICAL PROFILE AND IT'S OUTCOME

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CERTIFICATE

This is to certify that this dissertation entitled "**POST TRANSPLANT NEPHROTIC SYNDROME – CLINICO PATHOLOGICAL PROFILE AND IT'S OUTCOME"** *submitted by* **Dr.K.G. SIVAKUMAR**, *appearing for D.M. Nephrology Degree Examination in August 2007 is a bonafide record of work done by him under my direct audience and supervision in partial fulfillment of regulation of the Tamil Nadu Dr.M.G.R. Medical University, Chennai, I forward this to the Tamil Nadu Dr.M.G.R. Medical University, Chennai, Tamilnadu, India.*

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CONTENTS

BACKGROUND

Among the various factors that can affect the renal graft function, proteinuria of more than 1gm per day is one of the important factors in predicting graft outcome (6,7). Nephrotic range proteinuria is known to portend an even worse prognosis characterized by a markedly decreased graft survival rate. As per the previous data, 1 and 5 years graft survival of patients with Post transplant nephrotic syndrome (PTNS) were 75.3% and 37.5%, respectively (3,4) when compared with 87.5% and 52.5% for those without proteinuria (5).

Most of these data were studied before the usage of newer immunosuppression and newer biopsy criteria. Three major studies involving PTNS were conducted prior 1990 (1,2,5). Many data like predisposing factors, etiology and clinical course are unclear. There are no Indian studies in this regard.

AIM OF THE STUDY

1. To determine the incidence of Post Transplant Nephrotic Syndrome (PTNS).

2. To evaluate the renal graft histological patterns associated with PTNS.

3. To determine the effect of various causes of PTNS, on the graft survival outcome.

4. To analyze the predictors of graft outcome, among the PTNS subgroups.

MATERIALS AND METHODS

All the patients who underwent renal transplant between 1987 and 2004 at the department of Nephrology, Madras Medical College, were analyzed retrospectively.

After transplant, patients have scheduled follow up at our out patient department. The routine schedule include, once weekly follow up for initial 12 weeks followed by once in 2 weeks until 1 year. Beyond 1 year, patient is followed up once in a month until 5 years and, once in 3 months thereafter.

Prior to 1997, immunosuppression regimen at our department included high dose Steroids and Azathioprine. After 1997, Cyclosporine was introduced in the immunosuppression protocol. The protocol consists of Cyclosporine, given at a dose of 6mg/kg and Azathioprine at 2mg/kg, starting from day -1 of transplant. Steroid was started on day 0. Cyclosporine was tapered starting from 10 months post transplant and stopped at the end of 1 year.

During each visit routine investigations were performed. These investigations include:

1. Urine analysis

   - Specific gravity
   - pH
   - Protein
   - Sugar
   - Deposits
   - Protein Creatinine ratio (PCR)
   - 24 hours urinary protein, if PCR is more than 0.2

2. Hemogram

   - Total WBC count
   - Differential WBC count
   - Hemoglobin

- Packed cell volume
- ESR

3. Blood urea
4. Blood Sugar
5. Serum Creatinine
6. Serum Electrolytes
7. Monthly liver function test

Post transplant nephrotic syndrome (PTNS) is defined as absolute proteinuria of more than 3.0 gm/day associated with edema and hypoalbuminemia (16). In the presence of PTNS, graft biopsy was performed. Biopsy was performed using 16G Bard biopty gun. Biopsy sample was subjected to light microscopy and Immunoflouresence studies. Tissue was stained with Eosin and Hematoxylin, Periodic acid schiff, Masson Trichrome and Silver stains for light microscopy studies.

In patients with PTNS, following data were retrieved from their case records.

1. Age and gender of the patient
2. Native kidney disease
3. Donor status
4. Hypertension
5. Pretransplant proteinuria
6. Immunosuppression
7. Baseline proteinuria and serum creatinine following transplant
8. Post transplant time of PTNS onset
9. Presenting proteinuria and creatinine at PTNS onset Graft histology
10. Graft histology
11. Treatment of post transplant proteinuria
12. Response to treatment
13. Graft outcome
14. Follow up duration

STATISTICAL ANALYSIS

The following statistical analyses were used:

1. Chi-square test

2. Students T test

3. Levene's Test for Equality of Variances

4. Oneway Anova F test

5. Kaplan Meyer survival analyses

REVIEW OF LITERATURE

INCIDENCE:

Proteinuria following renal transplant may occur from various pathologies, with different graft survival. Several studies over the past decade have shown that proteinuria is both a diagnostic marker and a factor for progression of renal failure in native kidney disease as well as the transplanted kidney (7-10). Proteinuria after transplantation is a strong predictor of graft and patient survival(11) and is an independent risk factor for cardiovascular disease (12).

The problem in evaluating the post transplant proteinuria is the persistence of native kidney proteinuria. The delineation of the source of post-transplant proteinuria (native kidneys versus allograft) is important for appropriate management.

Proteinuria of allograft origin can develop in the early post-transplant period due to causes such as delayed graft function, acute rejection, calcineurin-inhibitor nephrotoxicity,

TTP/HUS syndrome and rapid recurrence of native renal disease (especially focal segmental glomerulosclerosis)(3). Early post-transplant proteinuria in a patient with residual native kidney urine output might be erroneously attributed to the native kidneys.

Studies were performed to evaluate the natural history of native kidney proteinuria in the post transplant period. Proteinuria of native kidney origin resolves within 1 to 10 weeks following successful transplantation with immediate graft function. Thus, beyond the immediate post-transplant period, proteinuria appears to be exclusively of allograft origin in live donor transplant recipients.

Whether similar resolution of proteinuria of native kidney origin occurs following deceased donor transplantation or whether delayed allograft function influences the time post-transplant at which proteinuria resolves remains to be established.

In the evaluation of native renal diseases, the urinary protein creatinine ratio (PCR) is increasingly replacing 24-h urine collection for quantifying protein excretion because the latter method is cumbersome and prone to collection errors. The reliability of the PCR as a surrogate for the 24-h urinary protein excretion is well established in both patients with native kidney diseases and in renal transplant recipients (13,14).

As per the previous studies nephrotic range proteinuria occurs in about 13% of the renal allograft recipient. It may develop at any period, from immediate postoperative period to many years post transplant.(15,16)

The major causes of PTNS in the previous studies were chronic allograft nephropathy, recurrent glomerulonephritis and de novo glomerular disease(1,16).

Recurrence and De novo glomerulonephritis (GN)

Glomerulonephritis (GN) is the cause of renal failure for 20 to 40% of those who receive a transplant; for these recipients, the threat of recurrent disease is real.

In the transplant setting factors like immunosuppression, different antigenic characteristics of the graft versus the native kidney, and different chronology may attenuate or prevent recurrence of some forms of GN. Despite these barriers, in few, the disease recurs and may result in allograft failure.

Allograft survival rates have steadily improved over the past 20 yr, largely as a result of our increasing ability to prevent and treat rejection (17). Recurrent GN is at present a minor contributor to allograft failure, responsible for 3% of all grafts lost in Australia and New Zealand from 1979 to 1998 and a similar number in the UK (18). However, the propensity for GN to recur seems to be time dependent (19). Thus, as graft survival increases, so, too, does the likelihood of disease recurrence.

As the average cadaveric graft is now projected to function for more than 13 yr and the average live-donor graft for more than 21 yr (17), we can expect to see an increased incidence of recurrent GN and a greater number of grafts failing as a result of recurrence.

By implication, the diagnosis of recurrent GN requires an accurate diagnosis of both the primary renal disease and subsequent disease in the transplant kidney (20,21). Although biopsy of native and transplant kidneys is simple, safe, and widely practiced, it is not performed in all cases of suspected GN in native or transplanted kidneys (22). Electron microscopy and immunohistology also are not routinely performed on transplant biopsies. Thus, the true incidence and impact of recurrent GN is not accurately known and is probably underestimated.

By implication, the diagnosis of recurrent GN requires an accurate identification and characterization of GN in the native kidney and subsequent identification of the same disease affecting the transplant kidney. These criteria mandate a renal biopsy of both native and transplant kidneys. Such criteria are not fulfilled in many cases of recurrent GN cited in the literature (22).

Patients who are presumed to have GN as the primary cause of renal failure and who go on to develop biopsy-proven

GN after transplantation are frequently labeled as having recurrent GN (24). Such patients may have either recurrent or de novo GN (24,25). Given this difficulty, many studies group de novo GN with recurrent GN.

Conversely, underdiagnosis of recurrent GN is also likely to be a major flaw in the literature, as many patients with the clinical features of deteriorating renal function and proteinuria posttransplantation are misclassified as having "chronic rejection" and are not biopsied or assessed adequately. Thus, the true incidence and impact of recurrent GN are not accurately known and are probably underestimated in the published literature (22).

Virtually all recognized forms of GN might recur post transplantation. Published data suggest that recurrent GN occurs in 6 to 19.4% of all renal transplant recipients, largely dependent on the time of assessment after transplantation (18,19,25,26), and causes the loss of 1.1 to 4.4% of all renal allografts (18,19,24,26).

The rate of recurrence and recurrence causing graft loss is obviously higher in patients with end-stage renal failure as a result of GN but varies enormously depending on the type of GN. For example, lupus nephritis recurs in fewer than 10% of cases and graft losses are uncommon, whereas recurrence is almost universal in cases of type II mesangiocapillary glomerulonephritis and graft losses are frequent. Although the impact of recurrent GN on graft survival depends on the type of GN, at a population level, the presence of recurrent GN clearly incurs an increased risk of graft failure (27).

Data from the USRDS demonstrate the negative impact of disease recurrence on graft survival, documenting a relative risk of 1.9 for graft loss at 5 yr as compared with those without recurrence (27).

Factors in addition to the underlying type of GN may influence the risk of recurrence. Time of follow-up clearly is important and may be related to the duration of exposure of the

graft to the nephritogenic factors that are responsible for causing GN (19).

In general, grafts that survive long term are exposed to nephritogenic factors for longer and are more likely to develop recurrent GN. This concept is borne out by registry data from the United States and ANZDATA. USRDS data show that the incidence of recurrent disease (glomerulonephritis and metabolic diseases) increases with duration of follow-up, from 2.8% at 2 yr to 9.8% at 5 yr and 18.5% at 8 yr of follow-up (27). As the overall duration of graft survival has improved (17), largely because of a decline in graft loss caused by rejection, the incidence of graft loss caused by recurrent disease paradoxically has increased.

In Australia, from the period 1979 to 1988 to the period 1989 to 1998, the incidence of all-cause graft loss fell by 45.5 per 1000 transplants, largely because of a fall in the incidence of graft loss caused by acute rejection, which fell by 28.5 per 1000 transplants. In contrast, the incidence of recurrent disease rose

by 1.3 per 1000. Consistent with these observations, the recipients of human leukocyte antigen (HLA)-identical transplants rarely experience rejection, they enjoy prolonged graft survival, but they have a high rate of recurrent GN (28).

Higher rates of recurrence have been reported in pediatric transplant recipients, in whom recurrent GN has been the cause of 6% of first allograft losses and 12% of subsequent graft losses (29). Patients who experience first allograft loss from recurrent GN are at higher risk of recurrence in a subsequent graft (24).

Recurrent Focal Segmental Glomerulosclerosis (FSGS)

A large number of series analyzed the post transplant recurrence of FSGS, because of the frequency of FSGS as a cause of end-stage renal failure and its widely recognized tendency to recur early and dramatically after transplantation. Recent studies at various centers have revealed patients with renal failure cause by FSGS incur a risk of recurrence of 20 to 30% for first transplants (31–33).

Proteinuria typically is early, occurring at a mean time of 14 d post transplantation in children (32), and is commonly manifest by heavy proteinuria, hypertension, and graft dysfunction. Patients with recurrent disease are more susceptible to acute rejection and acute renal failure (30), as well as graft loss, which occurs in 40 to 50% of cases (33). The rate of recurrence is more than 75% in subsequent grafts when the first graft was lost through recurrence (34).

Patients who are at highest risk of recurrence are those with an aggressive initial course characterized by renal failure within 3 yr of onset, age less than 15 yr, mesangial proliferation on biopsy, or recurrence in a previous transplant (31,32). Early reports focused on an apparent increase in recurrence after living related donation; however, subsequent reports have highlighted the safety of this approach (35,36).

Despite the contrary reports regarding the presence of permeability factors, removal of the permeability factor does

seem to be the mechanism responsible for the success of plasma exchange in the therapy of recurrent FSGS (37–39).

Although not assessed by a randomized, controlled, prospective trial, several series have reported the success of plasma exchange (or immunoadsorption) in inducing remission in the majority of patients treated within 2 wk of relapse (37,39,40).

Relapse after cessation of plasma exchange has been encountered but may be prevented or reversed by either chronic plasma exchange (40) or concurrent treatment with Cyclophosphamide (39). Recurrent FSGS is a feared complication but should not preclude transplantation in this group of patients. Live-donor transplantation probably should be reserved for those without features that suggest a high risk of recurrence.

De novo Focal Segmental Glomerulosclerosis (FSGS)

Histology of FSGS was commonly associated with other pathologies like chronic allograft nephropathy (CAN),

Cyclosporin toxicity, IgA nephropathy etc. These FSGS pathology, whether it is truly an isolated entity or end results of all chronic injuries, is still unclear. In an review by Cosio, among 1706 transplant kidney biopsies, 293 samples showed CAN, of which 30% had de novo FSGS. Diagnosis was made at a mean period of 57 months post transplant.

Only 24% of de novo FSGS had nephrotic range proteinuria and a mean 24 hours urinary protein was 2.4gm. However, histology of FSGS had important effect on graft survival. 5 years graft survival was 40% in the presence of de novo FSGS compared with 60% survival in CAN alone.

IgA nephropathy (IgAN)

IgAN is the most common form of GN that leads to end-stage renal failure, and patients who have this condition frequently receive transplants. Histologic recurrence is seen beyond 3 months posttransplantation (41). Most series have reported a histologic recurrence rate of 26 to 46% (42–46);

however, the only study in which all patients were biopsied found recurrence in 58% (41).

The clinical expression of disease is variable and time dependent. Reports on short-term graft survival in patients with IgAN have suggested an excellent graft survival rate for those who experience recurrence (24,46). The long-term consequences seem not so benign, as reported in five recent, substantial, retrospective, single-center reports of the clinical recurrence rate of IgAN and its impact on graft outcomes (41–45).

Mean follow-up in all series was approximately 5 yr, with renal biopsies performed as clinically indicated for investigation of graft dysfunction, hematuria, or proteinuria. Recurrence was detected in 26 to 46% of cases, resulting in or contributing to significant graft dysfunction or loss in 22 to 26% of cases. Graft loss during the first 3 yr posttransplantation was uncommon; however, functional impairment and eventual graft losses increased in number with longer follow-up, with recurrence

assuming progressively greater importance as a cause of graft failure over time.

In one series with an average follow-up of 61 months, the mean time to clinical recurrence was 31 months and to graft failure was 63 months (45); it is clear that with long-term follow-up, additional late recurrences may be expected and the mean time to events will increase. Recurrence is difficult to predict.

Patient characteristics-pretransplantation course (47), IgA structure, and angiotensin- converting enzyme (ACE) genotype (42)-have been found to have no predictive value. immunosuppression posttransplantation (cyclosporin or not) and posttransplantation course have no impact (41,42,47).

Timing of biopsy is critical; later biopsies are more likely to reveal IgA deposits (41). Living related donor transplantation has been associated with an increased risk of recurrence and graft loss in some series (45,47) but not in others (44). The increase in risk and the reduction in graft survival seem to be

small, however, and do not justify the avoidance of living related donor transplantation in patients with IgAN.

MEMBRANOUS GLOMERULONEPHRITIS

Data on recurrent membranous glomerulonephritis (MN) was clouded by two key issues—the paucity of reports involving significant numbers of patients and the frequency of de novo MN posttransplantation. The largest series reported a recurrence rate of 29% in 30 patients at 3 yr posttransplantation (49). The peak incidence of recurrence occurs at 3 years post transplant and plateaux for the next 7 years of follow up. The outcome of graft survival was poor as the graft loss was 38% at 5 years and 52% at 10 years of follow-up. This recurrence rate is higher than earlier estimates (22) but consistent with another recent study from Spain (47).

Management of recurrent MN is based on anecdotal reports and extrapolation of data on the management of native kidney MN. Spontaneous remissions, responses, and failures with immunosuppressive treatment all have been reported (47).

DE NOVO MEMBRANOUS GLOMERULONEPHRITIS (MGN)

De novo MGN is the second most common cause of PTNS, only next to chronic allograft nephropathy. De novo MN has been reported to occur in 2 to 9% of transplant recipients (48) and tends to present more insidiously and later than recurrent MN (48). The mean time of diagnosis was late at approximately 63 months post transplant and, as expected the incidence significantly increased with increased duration of follow up and graft survival. Interestingly, patients with de novo Membranous nephropathy did not differ much from the patients without membranous nephropathy, with regard to graft survival.

Mesangiocapillary glomerulonephritis (MCGN) Type I

MCGN type I seems to be mediated by glomerular deposition of immune complexes. Recurrence of disease is predictable and is seen in 20 to 33% of graft recipients (23). Graft loss has been reported in up to 40% of those with recurrence, and the risk of recurrence in subsequent grafts approaches 80% (23).

No form of treatment is proved. Recurrences related to persistent hepatitis B antigenemia may warrant a trial of lamivudine, although strong data are lacking. Other forms of MCGN type I have been treated with immunosuppression (51) and plasma exchange (52) with success in single cases.

MCGN Type II (Dense Deposit Disease)

MCGN type II has been found to recur in 50 to 100% of grafts (18,22,23,23). The clinical presentation typically shows hematuria and proteinuria during the first year after transplantation, with slowly declining renal function thereafter. Graft losses have been reported in 10 to 25% of recurrent cases, with male gender, crescents on biopsy, and heavy proteinuria indicating a higher risk of graft loss (18,22,23). No effective therapy is known.

Lupus Nephritis

The reported recurrence rate of lupus nephritis (LN) has varied from, 1 to 8% (18,53). Recurrence has been reported early (days) and late (years) after transplantation, with a mean time to recurrence of 3.1 yr in the largest series reported (53). Duration of dialysis before transplantation and serologic activity including ANA and complements, have not been found to predict recurrence (54).

The clinical and histologic pattern of recurrence is variable; Recurrence of all subtypes has been reported (54). In contrast to earlier reports, recent pooled data suggest that overall graft and patient survival may be worse in the lupus population, despite the younger age of lupus patients (54). Of nine reported series comparing transplant outcomes in lupus and non-lupus recipients, only three studies reported equivalent outcomes. The use of steroids, cyclophosphamide, and plasma exchange all has been reported in the treatment of reccurrence, with variable results (55).

Systemic Sclerosis/Scleroderma

A large retrospective analysis of patients reported to the UNOS registry after receiving a kidney transplant for scleroderma has been performed (56). Eighty-six patients reported between 1987 and 1997 were analyzed. Graft survival was 62% at 1 yr and 47% at 5 yr posttransplantation, and 24% of patients died during the 10-yr observation period (56).

Recurrence was responsible for graft loss in 21% of cases in which the cause was identified (18). No specific risk factor was associated with recurrence (56). The management of recurrent scleroderma is undefined. Overall, the posttransplantation course of scleroderma seems to be similar to that of lupus (56).

CHRONIC ALLOGRAFT NEPHROPATHY (CAN)

Chronic allograft nephropathy (CAN) is characterized by a relatively slow but variable rate of decline in renal function after the initial three post-transplant months, often in combination with proteinuria and aggravation or de novo appearance of hypertension(57). Linear regression analysis of the reciprocal of the serum creatinine concentration over time shows progressive of loss of function in more than 80% of patients with histologically proven chronic allograft nephropathy(58,59).

Twenty to 28% of patients with chronic allograft nephropathy have more than 0.5 g proteinuria per 24 hours compared with 6 to 8% of patients who do not have this condition(11). None of these clinical manifestations are specific, and other causes of graft dysfunction such as acute rejection, drug toxicity, or glomerulonephritis need to be excluded to make the diagnosis of chronic allograft nephropathy.

Risk factors associated with CAN:

Donor Factors	***Recipient Factors***	***Renal Events***
Living versus deceased	Age	Acute rejection
Age	Female sex	CMV disease
Female sex	African-American race	BK virus nephropathy
Vascular disease	Cause of renal disease	Doppler RI 0.80 or more
Glomerular disease	Diabetes mellitus	Proteinuria 800 mg/24 h
Cause of death	HLA matching	
Nephron mass	Panel reactive antibodies	
Ischaemic time	Blood pressure	
Delayed graft function	Compliance with treatment	

The histopathology of chronic allograft nephropathy is also not specific and consists of atherosclerosis, glomerular lesions and glomerular sclerosis, multilayering of the peritubular capillaries, interstitial fibrosis, and tubular atrophy.

Graft atherosclerosis consists of mostly concentric intimal thickening that affects large parts of arteries and arterioles, often accompanied by a moderate degree of infiltration of the vessel wall with macrophages, lymphocytes, and, to a much lesser extent, foam cells. The intimal thickening is thought to result from the migration of (myo)fibroblasts from the media into the intima, followed by local proliferation and deposition of extracellular matrix proteins.

The glomerular lesions of chronic transplant nephropathy are variable and include wrinkling and collapse of the glomerular tuft, glomerular hypertrophy(60), mesangial matrix expansion, and focal glomerulosclerosis(1).

In 1964, Hamburger et al described transplant glomerulopathy(61) as a lesion characterized by enlargement of the glomeruli, with swelling of the endothelial and mesangial cells, mesangiolysis, infiltration of the glomeruli with mononuclear cells, mesangial matrix expansion, and widening of

the subendothelial zone with interposition of mesangial cells and matrix(62).

Immunofluorescent studies of grafts with CAN show, in most cases, a nondiagnostic pattern of immunoglobulin deposition, although some cases show linear IgG deposits along the glomerular basement membrane or granular deposits of IgG or IgA in peripheral capillary loops(63). On electron microscopic examination, circumferential multilamellation of the peritubular capillary basement membranes is found in 80% of grafts with chronic allograft nephropathy(64).

Since 1991, there have been four international meetings in Banff, Canada, to standardize renal transplant pathology interpretations. Recent versions of the scheme deal in more detail with CAN. Recognizing that tubulointerstitial changes are most accurately sampled and appear to have prognostic significance(66), the grading of severity of chronic rejection focused initially on interstitial fibrosis and tubular atrophy, but

the most recent version includes grading of chronic glomerular and vascular changes(65).

HYPOTHESIS TO EXPLAIN CHRONIC ALLOGRAFT NEPHROPATHY

Tissue response to injury

Renal injury results in functional impairment and structural damage, followed by a stereotypic inflammatory response consisting of an influx of lymphocytes and monocytes, proliferation of tissue fibroblasts, deposition of extracellular matrix material, scar formation, and ultimately tissue restoration. Whereas ischemic damage and acute rejection episodes may resolve, irreversible fibrosis sometimes ensues.

A myriad of mediators, including proinflammatory cytokines, enzymes, and growth factors such as transforming growth factor-β (TGF-β), platelet-derived growth factor, interleukin-1β, tumor necrosis factor-α, angiotensin II, and

endothelin(67), seems involved in various stages of the inflammatory and tissue restoration responses.

Vascular versus interstitial injury

Because vascular rejection correlates most strongly with graft prognosis(68), the prevailing hypothesis to explain chronic allograft nephropathy is that the vascular injury initiates a sequence of events as described in the "response to injury" hypothesis(69). Vessel wall proliferation and vascular sclerosis result from growth-regulating cytokines produced by endothelial and smooth muscle cells in response to previous vessel wall injury, resulting in the activation of self-amplifying autocrine and paracrine activation cascades.

Cytokine excess theory

Chronic allograft nephropathy can be regarded as a process of excessive scar formation in response to injury, resulting in the disruption of the normal tissue architecture and function. It has been proposed that repetitive injury over a short period of time results in excessive production of fibrogenic

cytokines Genotypically high TGF- β producers seem at increased risk of losing their graft late after transplantation(70). Kidney transplants with CAN also have enhanced expression of urokinase plasminogen activator (uPA), its receptor, and plasminogen activator inhibitor type 1(71), and it is believed that uPA activates TGF- β.

Loss of supporting extracellular matrix architecture

The importance of disruptions of the three-dimensional extracellular matrix has received much attention in the recent days. Tubular epithelial cells must find an intact tubular basement membrane upon which to attach, to proliferate, and to organize their polarity; if they do not find this structure, they will undergo integrin-dependent apoptosis(72) or will perhaps transdifferentiate to fibroblasts(73).

Interleukin-1 or tumor necrosis factor, produced during tissue damage, can stimulate Fas expression in renal tubular cells(74). The expression of such a death receptor together with

FasL expression in neighboring tubular cells may induce apoptosis that results in tubular atrophy and interstitial fibrosis.

Premature senescence theory

Recently, it has been proposed that CAN represents an exhaustion or senescence of graft endothelial or tubular cells(75). Somatic cells in culture are limited in the number of cell divisions they can undergo, a phenomenon referred to as the Hayflick limit(76). After this finite number of divisions, they irreversibly shut down a number of processes such as replication and energy generation, and end in atrophy. The multitude of stresses that act on graft cells may lead to their premature senescence and consequent failure to exert their regulatory influence over a variety of functions such as tissue repair.

Many studies have been performed to assess the incidence of CAN and to identify the factors involved in the pathogenesis of this complication. In one single-center retrospective analysis of 2140 kidney transplant recipients, the 5-year incidence of biopsy-proven CAN was 12.2%. In this study, there were no

significant differences in CAN rates observed among cadaveric donor (13.2%), living related donor (nonidentical; 15.9%), and living unrelated donor (12.0%) kidney transplants. Overall, CAN was the cause of graft loss in 32% of failures: 28% cadaveric, 51% one-haplotype living related, 45% living unrelated, 25% identical. Overall, the development of CAN led to a 10.5-fold increase in graft loss.

RARE CAUSES OF PTNS

Acute rejection:

Proteinuria that develops within the first 3 month is usually associated with acute rejection (2,4,77,78, 80,81,83,84). In one study, 12 of 17 patients with mild proteinuria were found to have acute rejection (81). However, the degree of proteinuria reported with acute rejection is usually mild (81).

In another case reporting, the nephrotic syndrome with stable serum creatinine was the only manifestation of an acute rejection episode (85). In this patient, a renal transplant biopsy was performed and allograft biopsy revealed evidence of

glomerular rejection, as evidenced by glomerular cellular infiltrates in addition to vascular involvement. The prompt improvement of proteinuria observed with the treatment of rejection suggests that glomerulitis and vascular rejection may be associated with nephrotic range proteinuria.

Graft vein thrombosis

Few cases were reported in situation were proteinuria coexisted with renal graft vein thrombosis (2,4,82). All patients presented with sudden onset proteinuria in the first few weeks of post transplant period, with graft dysfunction and renal vein thrombosis. Most of the patients with graft vein thrombosis lost their graft.

RESULTS

Total number of renal transplants performed between 1989 and 2004 was 599. Among these, 61 patients developed nephrotic syndrome. There were 46 males (75.4%). Mean ages of male and female were 29.2 and 30.4 years, respectively. Among the study group, 44.3% of the patients had age group between 21 and 30 years.

All had live donor kidney transplantation. Mean donor age in this study was 42.6 years. Native kidney disease was not known in 16 patients (Table 2). Eight patients had biopsy proven glomerular disease prior transplant. In 29 patients who presented with contracted kidneys, basic kidney disease was presumed to be chronic glomerulonephritis (CGN) based on the presence of proteinuria, hypertension and gross edema. As a whole, 37 patients had CGN as their basic disease. Other causes were Obstructive nephropathy (1.6%), ADPKD (1.6%), benign nephrosclerosis (1.6%) and undetermined chronic interstitial

nephritis (4.9%). No statistical correlation exists between native kidney disease and PTNS.

Eight patients had pretransplant proteinuria of more than 2g/day. Mean 24 hours proteinuria in the immediate post transplant period was 0.203g. About seven patients had proteinuria more than 500 mg per day. Proteinuria resolved in these patients after 2 to 3 weeks of post transplant period. Mean serum creatinine in the immediate post transplant period was 89.72 µ/l. Thirty two patients received Cyclosporine based immunosuppression and twenty nine received Azathioprine/ Steroids as immunosuppressive therapy.

Mean duration of onset of post transplant nephrotic syndrome (PTNS) was 19.9 months. Mean age of patients with PTNS was 29.5 years

Chronic allograft nephropathy (CAN)

Among the 61 biopsies, 46 showed features of chronic allograft nephropathy. All these CAN biopsies revealed presence

of tubular atrophy and interstitial fibrosis. Variety of glomerular lesions was noted in CAN biopsies. Three showed evidence of enlarged glomeruli, lobulation and matrix expansion. Capillary walls showed areas of reduplication. In other biopsies glomeruli showed wrinkling, collapse of the glomeruli and segmental sclerosis.

Mean age of PTNS patients due to CAN was 29.6 years. 33 were males and 13 were females and their mean ages were 29.7 and 29.3 years, respectively (Table 3). In the CAN group, 9 had donor age less than 30 years, 23 had donor age between 31 and 50 years, and 14 had age more than 50 years.

Basic disease was known in 33 patients, among which CGN is the predominant cause. Mean post transplant baseline creatinine was significantly lower when compared to the de novo or recurrent GN group (85.80 vs 89.0 μ/l, $p = 0.001$). Mean post transplant baseline proteinuria was 0.198 g/day.

De novo or recurrent glomerulonephritis (GN)

De novo or recurrent glomerulonephritis (GN) occurred in 10 patients. IgA nephropathy (IgAN) was the commonest histology, followed by Focal segmental glomerulosclerosis (FSGS) and Membranous nephropathy (MGN). In this group, recurrent GN was proved in two patients. One had FSGS and the other had IgAN.

Mean age in this group was 27.7 years. There were 8 males and females were 2 with a mean age of 25.2 and 37.5 years, respectively. Donor age ranged between 32 and 48 years.

Miscellaneous histologies:

Two patients with acute cellular rejection presented with nephrotic proteinuria. One of these patients responded to antirejection therapy and proteinuria resolved following treatment. Other patient had worsening graft function despite treatment.

Two patients had CMV invasive disease involving the graft. CMV nephropathy occurred at a mean duration of 7.5 months.

Time of onset:

Mean duration of PTNS onset was 19.9 months. PTNS occurred at mean age of 29.5 years. PTNS occurred earlier in CAN group, compared to de novo or recurrent GN (mean duration: 21 vs 22.7 months). Among the de novo or recurrent GN group, FSGS had the earliest onset (mean duration: 2.0 +/- 1.7 months) and, IgAN occurred at a later period (mean duration: 37.3+/- 5.8 months), when compared to other GN (Table 4).

Mean proteinuria at the onset of PTNS, was higher in de novo or recurrent GN group (3.9 g/day p=0.001). In de novo or recurrent GN subgroup, maximum degree of proteinuria was present in FSGS group (4.3 g/day p=0.001).

Serum creatinine at the onset of PTNS, was higher in de novo or recurrent GN group when compared to CAN group (157.3 vs 154.3 µ/l). 90% of patients in GN group had Creatinine level more than 100 µ/l (Table 3).

Hypertension prevalence was 54.3% in CAN group and 70% in de novo or recurrent GN group.

Graft outcome

The mean duration of follow up was 36.8 months. Follow up was longer for CAN group compared to other de novo or recurrent GN group (37.6 vs 23.8 months). At the end of follow up, 19 grafts (31.2%) failed, 39(63.9%) were functioning and 3 lost to follow up. Graft failure rate was higher in de novo or recurrent GN compared to CAN group (50% vs 23.9%). Three years post transplant graft survival rates were 56% and 25% in CAN and de novo or recurrent GN, respectively (Figure 1).

Two years survival rate following PTNS onset was 13% and less than 5% in CAN and de novo or recurrent GN, respectively (Figure 2). Mean duration between PTNS onset and graft failure were11.7 and 20.8 in CAN and de novo or recurrent GN group, respectively. Among the de novo or recurrent GN group, FSGS had the earliest presentation (2.0 +/- 1.7 months) and poor outcome.

Comparing the graft functioning and failure patients in the CAN and de novo or recurrent GN group, no difference was found in terms of age, basic disease, donor age, and hypertension.

However, in de novo or recurrent GN group 80% of the surviving graft were on Cyclosporine based regimen whereas in CAN group, 54% of the surviving graft were on non-Cyclosporine regimen.

In both CAN and de novo or recurrent GN group, patient with failed graft had higher presenting creatinine and proteinuria at PTNS onset (Table 6).

DISCUSSION

Incidence of PTNS among the renal transplant recipients in this study is 10.2%. In most of the previous studies the incidence range between 3% and 13.7% (12,16,86). This difference in the incidence was due to varying criteria among the various studies. In the prior studies, only those patients, in whom proteinuria persisted for 1to 3 months, were included.

During the last 15 years, no change occurred in the incidence of PTNS. No correlations exist between the occurrence of PTNS and the baseline features like recipient and donor age, hypertension and immunosuppression protocol.

In the present study, CAN was the commonest cause of PTNS. This observation was similar to those findings reported in the pervious studies (12,16,,86). No particular histological lesion was associated with proteinuria.

Since most of the patients presented with advanced stages of CKD, pretransplant native kidney biopsy diagnosis could not be established. Hence post transplant GN was analyzed under one group. IgAN was the commonest histology in this group. In contrary, in Yakupogulu et al series minimal change histology was the commonest finding (16).

Recurrence of IgAN was documented in one patient. All de novo or recurrent IgAN patients developed PTNS beyond three years of post transplant. Among the de novo or recurrent GN patients, IgAN had the better survival.

Most of the de novo or recurrent GN patients, had evidence of CAN in the histological background. The contribution by each of the histologies to graft outcome is still unclear.

Three patients presented with FSGS, among whom one had proven recurrence. All the three patients had earlier onset of PTNS with significantly higher degree of proteinuria and poor graft survival.

Many CAN patients had evidence of focal sclerosis in their histology. Since they had predominant Glomerular, tubulointerstitial and vascular features suggestive of CAN, the sclerosis was thought to be consequence of hyperfiltration and chronic injury.

Interestingly, in this study two patients with PTNS had features of acute cellular rejection in biopsy. In one of these patients, proteinuria and graft function improved with anti rejection therapy. Similar presentation had been reported in various studies (2,4,77,78,79).

There is no definite treatment recommendation for PTNS. All the patients in this study were treated with ACE inhibitor. Remission could not be achieved in most of the patients.

Overall graft loss in patients due to PTNS was 31.1%. Survival rate was better in CAN group when compared to recurrent or de novo GN group. But, among the graft failure group, after the onset of PTNS, rapid worsening occurred in the

CAN patients. Two years survival rates following proteinuria were 13% and less than 5%, in CAN and recurrent or de novo GN group, respectively.

In recurrent or de novo GN group, patients on Cyclosporine based immunosuppressive regimen had better graft outcome. In contrary, in CAN group, graft outcome was not significantly affected by difference in immunosuppressive regimens.

Analyzing other factors influencing graft outcome, presenting proteinuria and creatinine at PTNS onset were higher in patients with failed graft. These findings were similar in all subgroups of PTNS.

This study had two major drawbacks. Due to small sample size, beta error could occur in subgroup analysis of recurrence or de novo GN group.

Because of the same reason, statistical significance could not be derived in subgroup analysis. Since the basic disease was not known in most of the patients, GN group could not be stratified and their outcome difference was not studied.

CONCLUSIONS

1. The incidence of PTNS was 10.2%.

2. PTNS occurred at a mean duration of 20 months following transplant.

3. CAN was the commonest cause of PTNS.

4. IgA nephropathy was the commonest cause of PTNS among the recurrent or de novo GN group.

5. FSGS occurred earliest and had poorer outcome among the recurrent or de novo GN group.

6. Graft loss occurred in one third of the patients with PTNS.

7. Graft loss was more common in recurrent or de novo GN group when compared to CAN group.

8. Higher presenting serum creatinine and proteinuria at the onset of PTNS were associated with adverse graft outcome.

9. Following PTNS onset, two years graft survival rates were 13% and less than 5% in the CAN and recurrent or de novo GN group, respectively.

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S.No	Name	Age (years)	Sex	NC.No	Basic kidney disease	Basic proteinuria (gm/day)	Donor age (years)	Donor relationship	Hypertension	Date of transplant	Immuno-suppression	Baseline proteinuria post transplant (gm/day)	Baseline creatinine post transplant (µ/l)
1	Krishnan	32	Male	2305/94	Not known	2.4	50	Mother	No	5.23.1995	PDN/AZA	2	96
2	Ramesh	22	Male	145/94	CGN unclassified	1.7	39	Mother	Yes	12.6.1994	PDN/AZA	0.6	81
3	Bharathi	19	Female	1026/88	MPGN	2.2	40	Mother	Yes	4.13.1989	PDN/AZA	0	81
4	Manoharan	18	Male	56/89	MPGN	2.8	35	Mother	No	6.1.1989	PDN/AZA	0	80
5	Kennady	27	Male	2160/92	Not known	1.4	23	Sister	No	9.21.1993	PDN/AZA	0	70
6	Kannan	22	Male	432/89	Not known	3.2	40	Mother	Yes	8.24.1989	PDN/AZA	0	81
7	Karunammal	35	Female	1047/88	Not known	0.8	53	Aunt	Yes	3.2.1989	PDN/AZA	0	88
8	Shanmuga sundaram	18	Male	898/89	Not known	0.4	54	Mother	Yes	15.9.1989	PDN/AZA	0	88
9	Ummar	23	Male	222/89	Not known	0.9	40	Mother	No	8.17.1989	PDN/AZA	0	78
10	Bagya lakshmi	14	Female	1472/92	Not known	1.6	41	Mother	No	12.4.1993	PDN/AZA	0.3	83
11	Anjanelu	37	Male	1610/92	CIN unclassified	0.2	52	Mother	Yes	3.5.1993	PDN/AZA	0	130
12	Murugan	30	Male	349/93	Not known	1.6	55	Mother	No	8.24.1993	PDN/AZA	0.7	77
13	Shanmugam	27	Male	647/93	CGN unclassified	2.8	50	Father	Yes	8.10.1993	PDN/AZA	0.2	70
14	Kavitha	27	Female	253/89	CGN unclassified	1.3	50	Father	No	22.12.1993	PDN/AZA	0.4	88
15	Poongodi	25	Female	1703/92	CGN unclassified	1.4	55	Mother	No	4.13.1993	PDN/AZA	1.4	100
16	Raja	32	Male	1203/93	CGN unclassified	3.6	55	Mother	Yes	9.9.1993	PDN/AZA	0.3	88
17	Manickam	26	Male	128/93	CGN unclassified	3.8	45	Mother	Yes	3.8.1993	PDN/AZA	0.2	70
18	Jayaraman	35	Male	128/88	Not known	0.2	30	Cousin	Yes	6.9.1988	PDN/AZA	0	86
19	Naveen	18	Male	332/88	Obstructive nephropathy	0.7	38	Mother	No	4.12.1988	PDN/AZA	0.6	88
20	Saroja	45	Female	128/87	Benign nephrosclerosis	0.4	19	Mother	Yes	8.13.1987	PDN/AZA	0.2	86
21	Annakili	28	Female	1296/88	Not known	0.8	28	Cousin	Yes	5.4.1989	PDN/AZA	0	100
22	Gajendran	32	Male	396/92	CGN unclassified	1.8	32	Brother	Yes	2.9.1993	PDN/AZA	0.1	77
23	Ravichandran	27	Male	564/93	FSGN	1.4	48	Mother	Yes	7.20.1993	PDN/AZA	1.8	63
24	Chitra	38	Female	621/90	Not known	0.6	45	Mother	Yes	5.7.1991	PDN/AZA	0	77
25	Rambai	30	Female	1325/91	Not known	0.2	26	Cousin	Yes	28.2.1992	PDN/AZA	0.7	88
26	Elavaraj	36	Male	179/91	Not known	1.8	40	Cousin	Yes	6.6.1991	PDN/AZA	0.5	88
27	Saravanan	20	Male	1490/89	Obstructive nephropathy	2.4	39	Mother	Yes	13.3.1990	PDN/AZA	0.5	88
28	Sabu	22	Male	1493/94	Not known	0.4	42	Mother	Yes	4.8.1995	PDN/AZA	0.4	81
29	Padmanaban	25	Male	2351/01	CGN unclassified	1.2	35	Brother	No	19.3.2002	CSA/PDN/AZA	0.2	88
30	Mohanagurusamy	17	Male	1347/99	CGN unclassified	0.8	47	Mother	Yes	24.9.1999	CSA/PDN/AZA	0.1	88
31	Maheswar	20	Male	2126/04	FSGS	4.2	41	Mother	No	2.11.2004	CSA/PDN/AZA	0	88

S.No	Name	Age (years)	Sex	NC.No	Basic kidney disease	Basic proteinuria (gm/day)	Donor age (years)	Donor relationship	Hypertension	Date of transplant	Immuno-suppression	Baseline proteinuria post transplant (gm/day)	Baseline creatinine post transplant (µ/l)
32	Jebakirubi	37	Female	126/03	CGN unclassified	1.8	37	Sister	No	29.9.2003	CSA/PDN/AZA	0	88
33	Geethalakshmi	32	Female	1169/01	CGN unclassified	1.9	52	Mother	No	7.8.2001	CSA/PDN/AZA	0	88
34	Thangathilagam	44	Female	85/01	CGN unclassified	1.4	42	Brother	Yes	17.4.2001	CSA/PDN/AZA	0.1	88
35	Kamalakannan	36	Male	1720/93	CIN unclassified	0.3	54	Mother	Yes	23.6.1994	PDN/AZA	0.2	88
36	Dhanajeyan	53	Male	884/00	CGN unclassified	1.2	32	Daughter	No	8.8.2002	CSA/PDN/AZA	0.2	86
37	Vivekanandan	32	Male	1791/04	CGN unclassified	1.6	55	Mother	No	29.9.2004	CSA/PDN/AZA	0.3	88
38	Irudhayarag	28	Male	317/02	CGN unclassified	1.4	24	Sister	No	23.5.2002	CSA/PDN/AZA	0.1	88
39	Lakshmi	27	Female	3171/04	MGN	1.8	50	Mother	Yes	15.11.2004	CSA/PDN/AZA	0	88
40	Udayakumar	42	Male	3747/04	DPGN	0.8	56	Mother	No	24.3.2004	CSA/PDN/AZA	0	96
41	Chelladurai	49	Male	1309/01	CGN unclassified	0.8	21	Son	No	26.8.2002	CSA/PDN/AZA	0	88
42	Periasamy	30	Male	2421/04	CGN unclassified	1.8	57	Father	No	30.3.2004	CSA/PDN/AZA	0	88
43	Ravi	49	Male	2591/04	CGN unclassified	1.6	40	Brother	Yes	23.1.2004	CSA/PDN/AZA	0	88
44	Thrivengadam	32	Male	276/97	IgAN	1.6	36	Sister	Yes	24.6.1997	PDN/AZA	0	88
45	Punithalakshmi	27	Female	1119/96	Aorto arteritis	0.3	52	Father	No	28.8.2001	CSA/PDN/AZA	0	88
46	Subramani	42	Male	2269/00	Not known	0.2	54	Sister	Yes	21.11.2000	CSA/PDN/AZA	0	86
47	Ramesh	20	Male	447/97	CGN unclassified	2.4	40	Mother	Yes	10.6.1997	PDN/AZA	0	77
48	Sasikanthan	23	Male	2530/02	CGN unclassified	1.7	43	Mother	Yes	23.1.2003	CSA/PDN/AZA	0	88
49	Selvakumar	22	Male	1073/03	CGN unclassified	1.6	42	Mother	Yes	9.9.2003	CSA/PDN/AZA	0	86
50	Kuttan	40	Male	472/00	CGN unclassified	1.8	26	Sister	Yes	18.7.2000	CSA/PDN/AZA	0	88
51	Vishnu	19	Male	2584/01	CGN unclassified	1.4	35	Mother	Yes	4.4.2002	CSA/PDN/AZA	0	88
52	Kousalya	28	Female	1809/02	ADPKD	0.8	50	Mother	Yes	19.12.2002	CSA/PDN/AZA	0	88
53	Karthick	22	Male	435/03	FSGS	3.6	42	Mother	Yes	18.8.2003	CSA/PDN/AZA	0.1	88
54	Chinnapparaj	29	Male	2649/02	CGN unclassified	1.8	50	Father	Yes	11.3.2003	CSA/PDN/AZA	0.2	88
55	Ramu	34	Male	1462/03	CGN unclassified	1.7	50	Father	Yes	24.2.2004	CSA/PDN/AZA	0	130
56	Sivakumar	28	Male	2362/03	CGN unclassified	1.8	51	Father	Yes	21.8.2001	CSA/PDN/AZA	0	88
57	Neelavannan	38	Male	2308/99	IgAN	1.4	48	Brother	Yes	22.4.2002	CSA/PDN/AZA	0	88
58	Balamurugan	25	Male	306/03	CGN unclassified	1.4	55	Mother	Yes	9.3.2004	CSA/PDN/AZA	0	88
59	Velmurugan	28	Male	2014/04	CGN unclassified	1.3	52	Mother	Yes	6.12.2004	CSA/PDN/AZA	0	228
60	Kamaraj	22	Male	2289/02	CGN unclassified	1.2	40	Mother	Yes	28.1.2003	CSA/PDN/AZA	0	120
61	Loganathan	32	Male	1741/04	CIN unclassified	0.6	28	Sister	Yes	19.10.2004	CSA/PDN/AZA	0	88

S.No	Name	Duration of PTNS onset (months)	Proteinuria at PTNS onset (gm/day)	Presenting creatinine (µ/l)	Highest creatinine (µ/l)	Graft histology	Immouno -fluorosence	Graft loss duration after transplant	Graft loss duration after PTNS onset	Follow up (months)
1	Krishnan	1	3	170	486	Acute rejection	No deposits	4 months	3 months	4
2	Ramesh	6	3	110	189	CAN	IgM,C3	functioning graft	functioning graft	28
3	Bharathi	8	3.1	156	386	CAN	No deposits	functioning graft	functioning graft	32
4	Manoharan	9	3.2	136	309	CAN	IgM,C3	functioning graft	functioning graft	34
5	Kennady	11	3	156	300	CAN	IgM,C3	functioning graft	functioning graft	9
6	Kannan	20	3.2	230	581	CAN	IgG,IgM,C3	9 months	8 months	29
7	Karunammal	14	3	168	344	CAN	IgG,IgM,C3	functioning graft	functioning graft	46
8	Shanmuga sundaram	16	3	110	154	CAN	IgG,IgM,C3	functioning graft	functioning graft	38
9	Ummar	23	3.2	158	242	CAN	IgG,IgM,C3	functioning graft	functioning graft	52
10	Bagya lakshmi	15	3.2	186	364	CAN	IgM,C3	functioning graft	functioning graft	32
11	Anjanelu	13	3.2	188	376	CAN	IgG,IgM,C3	functioning graft	functioning graft	42
12	Murugan	12	3.2	156	328	CAN-Transplant glomerulopathy	IgM,C3	functioning graft	functioning graft	34
13	Shanmugam	17	3	124	189	CAN	IgG,IgM,C3	functioning graft	functioning graft	44
14	Kavitha	24	3.1	156	188	CAN	IgM,C3	functioning graft	functioning graft	54
15	Poongodi	12	3.2	178	444	CAN-Transplant glomerulopathy	No deposits	46 months	22 months	46
16	Raja	11	3	158	216	CAN	IgM,C3	functioning graft	functioning graft	26
17	Manickam	22	3.1	210	582	CAN	IgM,C3	23 months	1 month	23
18	Jayaraman	9	3.05	186	449	CAN-Transplant glomerulopathy	IgM,C3,c1q	functioning graft	functioning graft	33
19	Naveen	24	3.2	246	540	CAN	IgM,C3	18 months	4 months	18
20	Saroja	7	3.3	146	312	CAN	IgG,IgM,C3	46 months	39 months	46
21	Annakili	3	3	146	297	CAN	IgG,IgM,C3	functioning graft	functioning graft	18
22	Gajendran	18	3.2	82	98	CAN	IgM,C3	functioning graft	functioning graft	56
23	Ravichandran	22	3.1	82	84	CAN	IgG,IgM,C3	functioning graft	functioning graft	66
24	Chitra	9	3.8	186	243	MPGN	IgM,IgA,C3	functioning graft	functioning graft	22
25	Rambai	12	3	234	390	CAN	IgM,C3	functioning graft	functioning graft	30
26	Elavaraj	34	4.3	186	388	IgAN	IgG,IgM,C3	lost follow up	lost followup	58
27	Saravanan	32	4	224	414	MGN	IgM,C3	lost follow up	lost followup	44
28	Sabu	20	3	186	347	CAN	IgM,C3	lost follow up	lost followup	36
29	Padmanaban	31	3.9	234	572	IgAN	IgA,IgM,C3c	42 months	12 months	53
30	Mohanagurusamy	38	3	256	710	CAN	IgG,IgM,C3	46 months	8 months	46
31	Maheswar	15	3	110	131	CAN	IgG,IgM,C3	functioning graft	functioning graft	17

S.No	Name	Duration of PTNS onset (months)	Proteinuria at PTNS onset (gm/day)	Presenting creatinine (µ/l)	Highest creatinine (µ/l)	Graft histology	Immouno -fluorosence	Graft loss duration after transplant	Graft loss duration after PTNS onset	Follow up (months)
32	Jebakirubi	1	3.4	100	105	FSGS	IgG,IgM,C3	functioning graft	functioning graft	10
33	Geethalakshmi	24	3	136	208	CAN	IgG,IgM,C3	functioning graft	functioning graft	10
34	Thangathilagam	27	3.2	186	526	CAN	IgG,IgM,C3	62 months	20 months	62
35	Kamalakannan	10	3	92	102	CAN	IgG,IgM,C3	functioning graft	functioning graft	156
36	Dhanajeyan	7	3	86	110	CAN	IgG,IgM,C3	functioning graft	functioning graft	14
37	Vivekanandan	11	3.3	146	254	CAN	IgG,IgM,C3	functioning graft	functioning graft	20
38	Irudhayarag	28	3.1	186	260	CAN	IgM	functioning graft	functioning graft	53
39	Lakshmi	8	3.6	186	256	CAN	IgG,IgM,C3	functioning graft	functioning graft	16
40	Udayakumar	1	3	198	343	HUS	IgM,C3c	functioning graft	functioning graft	1
41	Chelladurai	30	3	100	120	CAN	IgM,C3c	functioning graft	functioning graft	32
42	Periasamy	28	3.2	210	526	CAN	IgM,C3c	31 months	3 months	31
43	Ravi	7	3.2	90	90	CAN	IgM,C3c	functioning graft	functioning graft	13
44	Thrivengadam	90	3	96	100	CAN	IgG,IgM,C3	functioning graft	functioning graft	116
45	Punithalakshmi	62	3	146	195	CAN	IgG,IgM,C3	functioning graft	functioning graft	64
46	Subramani	25	3.1	110	123	CAN	IgG,IgM,C3	functioning graft	functioning graft	34
47	Ramesh	1	4.8	234	580	FSGS	IgM,C3c	10 months	9 months	10
48	Sasikanthan	19	3.4	134	169	CAN	IgM,C3c	functioning graft	functioning graft	51
49	Selvakumar	9	3	164	280	CMV inclusions	IgM	functioning graft	functioning graft	10
50	Kuttan	58	3.2	110	123	CAN	IgG,IgM,C3	functioning graft	functioning graft	82
51	Vishnu	31	3.9	156	260	MGN	IgG,IgM,IgAC3	functioning graft	functioning graft	40
52	Kousalya	9	3.2	88	88	CAN	IgM	functioning graft	functioning graft	24
53	Karthick	4	4.6	186	600	FSGS	IgM,C3c	26 months	22 months	26
54	Chinnapparaj	43	3	256	580	CAN	IgG,IgM,C3	44 months	1 month	48
55	Ramu	4	3.2	186	487	CMV inclusions	IgM	6 months	2 months	19
56	Sivakumar	47	3	168	240	CAN	IgG,IgM,C3	functioning graft	functioning graft	24
57	Neelavannan	44	3.9	124	140	IgAN	IgA,IgM,C3c	functioning graft	functioning graft	58
58	Balamurugan	20	3	146	350	CAN	IgM,C3c	functioning graft	functioning graft	29
59	Velmurugan	2	3	158	648	Acute rejection	IgM	3 months	3 months	2
60	Kamaraj	40	3.2	148	205	IgAN	IgA,IgM,C3c	functioning graft	functioning graft	48
61	Loganathan	14	3	234	800	CAN	IgG,IgM,C3	14 months	1months	24